REMARKS

Applicant has received and reviewed the Office Action dated February 15, 2007. By way of response, Applicant has canceled claims 16-26, 28-30, and 32-79 without prejudice and has amended claims 1, 12, 14, and 80. No new matter is presented. Applicant submits that the pending claims are supported by the specification.

For the reasons given below, Applicant submits that the pending claims are in condition for allowance and notification to that effect is earnestly solicited.

Restriction Requirement

Applicant acknowledges that the restriction and species election requirements have been made final.

Priority Information

The Examiner has requested that Applicant amend the first paragraph of the present specification to indicate that the present application is a continuation in part of Application Serial No. 10/244,727. Applicants respectfully submit that the first paragraph of the present specification states that the present application is a continuation in part of Application Serial No. 10/244,727 and a PCT application.

Rejection of Claims Under 35 U.S.C. § 112

The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 112, second paragraph. Without acquiescing to the rejection and solely to expedite allowance of the claims, each of claims 1, 12, 14 and 80 have been amended to include a recitation suggested by the Examiner. Withdrawal of the rejection is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 102

1. The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 102(b) as anticipated by Korbel et al., *J. Am. Chem. Soc.* **123**: 361–62 (2001). Applicants respectfully traverse this rejection.

Independent claims 1 and 80 recite a method of making a heterogeneous building block array including applying building blocks to a solid support to produce spots in which "a first spot

comprises a first combination of building blocks and a second spot comprises a second combination of building blocks." Independent claims 12 and 14 recite a method of making a receptor or receptor surface in which 2 or more of the different building blocks together form a candidate artificial receptor, a lead artificial receptor, a working artificial receptor, or a combination thereof.

Each spot in the array produced by the method of Korbel et al. includes the same enantiomeric compound and dyes (Scheme 1, page 361). Therefore, the Korbel et al. reference neither teaches nor suggests the presently claimed methods.

The Korbel et al. reference employs an array system for determining enantiomeric excess produced by enantioselective catalysts and reactions. Enantiomers of a single molecule are bound to a spot in an array. The enantiomers react at different rates with chiral dyes. These different reaction rates produce different colors in spots with different ratios of the enantiomers of the single molecule. Through use of standards, the ratios of the colors can be correlated with ratio of the enantiomers (the enantiomeric excess).

Equations provided in the Korbel et al. reference convert the ratios of colors to the percent enantiomeric excess (% ee) (page 361, column 2, equation (1), and paragraph bridging pages 361-362). Factor "s" is defined in this equation as a ratio of rate constants. This ratio treats the rate constants as independent as one another. That is, the reaction of one enantiomer bound to the array does not affect the reaction of the other enantiomer. Put another way, the enantiomers do not cooperate with one another and they are not in proximity to one another forming an artificial receptor or receptor surface. Therefore, for yet another reason, the Korbel et al. reference neither teaches nor suggests the presently claimed methods.

Further, as described above, the method of Korbel et al. would produce the same result if the enantiomers were placed in a solution in a container, such as a tube or well. The product obtained by enantioselective catalysis or reaction is in one container. Each standard is in its own container. The color obtained in each container is compared to determine the enantiomeric excess from the reaction or catalyst. Korbel et al. chose a spot on an array as a container as a matter of convenience.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the Korbel et al. reference neither teaches nor suggests the presently claimed methods, and withdrawal of this rejection is respectfully requested.

2. The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 102(b) as anticipated by Maly et al., *Proc. Natl. Acad. Sci.* **97**: 2419–24 (2000). Applicants respectfully traverse this rejection.

The Office Action directs our attention to passages of the Maly et al. reference relating to the method illustrated in Figure 1 and employing compounds shown in Table 2.

The Maly et al reference discloses the method of Figure 1 at page 2419, paragraph bridging columns 1 and 2. This paragraph states:

> (1) A set of potential binding elements is prepared wherein each molecule of the set must be soluble in aqueous solution at high concentrations and must incorporate a common chemical linkage group. (2) The set of potential binding elements is screened at high concentrations (≥1 mM) to identify all binding elements that interact even weakly with the biological target. (3) A combinatorial library of linked binding elements is prepared whereby the binding elements are connected by using the common chemical linkage groups through a set of flexible linkers. (4) The Combinatorial library of linked binding elements is screened to identify the tightest-binding ligands.

Many features distinguish the present invention from this disclosure. For example, the present claims recite "independently coupling the different building blocks to the solid support". Figure 1 and Table 2 of the Maly et al. reference do not disclose spots, coupling building blocks in spots, a solid support, and so on. Therefore, the Maly et al. reference neither teaches nor suggests the presently claimed methods.

The Office Action asserts that the Maly et al. reference discloses a molecular complex bound to a well of a microtiter plate. According to the Office Action, the molecular complex includes:

avidin-biotin-peptide-kinase

and/or

avidin-biotin-peptide-kinase-kinase inhibitor.

It is apparently asserted that either molecular complex represents a plurality of building blocks bound to a support.

Applicant respectfully disagrees. The asserted molecular complexes would represent a single building block bound to the support. Further, each of the present independent claims recites a method including "independently coupling the different building blocks to the solid support". That is, each different building block is coupled to the support. The building blocks

are not coupled to one another, as in the scenario described in the Office Action. Therefore, the Maly et al. reference neither teaches nor suggests the presently claimed methods.

Applicant also respectfully asserts that the Maly et al. reference describes a kinase assay in which the molecular complex bound to the support:

avidin-biotin-peptide

is a kinase substrate. In the presence of the kinase this complex is converted to

avidin-biotin-phosphorylated peptide.

The phosphorylated peptide is then detected in an ELISA assay, which produces color. This phosphorylation is an enzyme catalyzed reaction. Enzyme catalyzed reactions include formation of an enzyme:substrate complex. In this case, the enzyme:substrate complex would be avidin-biotin-peptide-kinase. However, this complex would be extremely short lived and would not form an entity analogous to a building block.

The Office Action seems to suggest that the method of Maly et al. would form a complex including avidin-biotin-peptide-kinase-kinase inhibitor. In fact, according to typical enzyme inhibition patterns, the inhibitor prevents formation of the enzyme:substrate complex. That is, in the system of Maly et al., the inhibitor would prevent the kinase from binding to the peptide. The complex formed would be kinase-kinase inhibitor. The inhibitors would not bind to the avidin-biotin-peptide complex. Maly et al. are searching for inhibitors that bind to the kinase, not the microtiter plate and peptide.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the Maly et al. reference neither teaches nor suggests the presently claimed methods, and withdrawal of this rejection is respectfully requested.

3. The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 102(b) as anticipated by Shao et al., *J. Org. Chem.* **61**: 6086–87 (1996). Applicants respectfully traverse this rejection.

The Office Action asserts that the Shao et al. reference discloses a molecular complex bound to a polystyrene bead. According to the Office Action, the molecular complex includes:

bead-acylated tripeptide-putative receptor

and/or

bead-acylated tripeptide-putative receptor-dye.

It is apparently asserted that the molecular complex represents a plurality of building blocks bound to a support. It is also asserted that this system produces a plurality of spots on a polystyrene bead.

Applicant respectfully disagrees. The asserted molecular complexes would represent a single building block bound to the support. Further, each of the present independent claims recites a method including "independently coupling the different building blocks to the solid support". That is, each different building block is coupled to the support. The building blocks are not coupled to one another, as in the scenario described in the Office Action.

Applicants also respectfully assert that the Shao et al. reference describes a system including:

bead-acetylated peptide

which can form:

bead-acetylated peptide-putative receptor.

Each bead or group of beads is incubated with a single putative receptor (Shao et al., page 3086, column 2, third full paragraph). Thus, only one complex is formed on each bead. The system of Shao et al. does not produce a plurality of spots on a bead.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the Shao et al. reference neither teaches nor suggests the presently claimed methods, and withdrawal of this rejection is respectfully requested.

4. The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 102(b) as anticipated by Pirrung, *Chem. Rev.* **97**: 473–88 (1997). Applicants respectfully traverse this rejection.

The Office Action asserts that the Pirrung reference discloses making peptides bound to a microtiter plate. It is asserted that a single peptide bound to a microtiter plate includes a plurality of building blocks bound to the well of the microtiter plate. Applicant respectfully disagrees. A peptide bound to a microtiter plate would represent a single building block bound to the plate. Further, each of the present independent claims recites a method including "independently coupling the different building blocks to the solid support". That is, each different building blocks is coupled to the support. The building blocks are not coupled to one another, as in the scenario described in the Office Action. Therefore, the Pirrung reference neither teaches nor suggests the presently claimed methods.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the Pirrung reference neither teaches nor suggests the presently claimed methods, and withdrawal of this rejection is respectfully requested.

5. The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 102(b) as anticipated by Balch, U.S. Patent No. 6,083,763. Applicants respectfully traverse this rejection.

The Office Action asserts that the Balch reference discloses (e.g., at column 37, lines 15-47) spots including a plurality of building blocks. This portion of the Balch reference relates to an embodiment illustrated in Figure 17. In fact, the Balch reference describes and illustrates spots that include only a single hapten or drug. Balch makes a plurality of homogeneous spots in a single well of a microtiter plate. This is not a heterogeneous spot or region. Therefore, the Balch reference neither teaches nor suggests the presently claimed methods.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the Balch reference neither teaches nor suggests the presently claimed methods, and withdrawal of this rejection is respectfully requested.

6. The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 102(b) as anticipated by New et al., WO 01/001140. Applicants respectfully traverse this rejection.

The Office Action asserts that the New et al. reference discloses lipid conjugates of amino acids in a liposome and coupling those liposomes to a support. Applicants respectfully submit that this disclosure is distinct in several ways from the presently claimed invention.

First, if we consider the individual conjugates to be building blocks, then the Office Action would assert that a plurality of conjugates in a liposome with the liposome bound to a microtiter plate represents a plurality of building blocks bound to the well of the microtiter plate. Applicant respectfully disagrees. A liposome bound to a microtiter plate would represent a single building block bound to the plate. Further, each of the present independent claims recites a method including "independently coupling the different building blocks to the solid support". That is, each different building block is coupled to the support. The building blocks are not coupled to a liposome, as in the scenario described in the Office Action. Therefore, the New et al. reference neither teaches nor suggests the presently claimed methods.

Second, the New et al. reference discloses employing each liposome-conjugate singly. Liposomes including different mixtures of conjugates are never mixed according to New et al. Thus, coupling the single liposome-conjugate to a microtiter plate produces a feature that resembles a homogeneous spot. Each thing bound to the plate (i.e., each liposome conjugate) is the same. This would not be a plurality of different building blocks bound to the plate. Therefore, the New et al. reference neither teaches nor suggests the presently claimed methods.

Third, immobilization is merely another way to contain the liposomes. The result of using the liposome is the same whether it is in solution or immobilized. Accordingly, plate bound liposomes are not in proximity to one another. Therefore, the New et al. reference neither teaches nor suggests the presently claimed methods.

Fourth, in the context of the present invention, Applicant respectfully suggests a different view of New et al. New et al. employ liposomes in solution and test ligands bound to a support. The present invention employs building blocks bound to a support to form artificial receptors that can be used to bind test ligands that are in solution.

This orientation, test ligand in solution rather than on support, is one of the advantageous features of the present method. Employing combinations of building blocks with the building blocks independently coupled to the support (and with test ligand in solution) provides a far simpler and less labor intensive method for making very large numbers of artificial receptors. The liposomes are laboriously made one at a time for individual screening against a test ligand bound to a support.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the New et al. reference neither teaches nor suggests the presently claimed methods, and withdrawal of this rejection is respectfully requested.

7. The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 102(b) as anticipated by Stålberg, WO 93/025910. Applicants respectfully traverse this rejection.

The Office Action asserts that the Stalberg reference discloses a sensing surface area including a plurality of antibodies. Each of the antibodies is itself a known, natural receptor that is produced and coupled to the surface. The surface can then be employed to detect one or more known ligands for the antibodies employed. This is a conventional antibody system as known in the art. This is not a heterogeneous spot.

The present method also differs in other respects. The present building blocks are not antibodies. The present building blocks are each independently bound to the support and together form an artificial receptor. The antibodies in Stalberg do not together form an artificial receptor. The antibodies are not in proximity to one another.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the Balch reference neither teaches nor suggests the presently claimed methods, and withdrawal of this rejection is respectfully requested.

8. The Examiner rejected claims 1–3, 10–15 and 80 under 35 U.S.C. § 102(e) as anticipated by Lahiri et al., US2003/0138853. Applicants respectfully traverse this rejection.

Lahiri describes an array with a plurality of biological membrane microspots on a substrate. The microspots consist of membrane-bound proteins coupled to a solid support. Furthermore, Lahiri notes that it is typical for a microspot to contain only one type of protein, and the protein in one microspot differs from the proteins on a second microspot.

The Examiner contends that "in certain situations more than one type of protein is included in each microspot." Applicants submit that this is different from the plurality of building blocks coupled to a single spot, as in the present claims. Lahiri states that more than one protein is present where the membrane-bound protein exists as a heterodimer. If the protein is considered equivalent to a building block of the present claim, then Lahiri teaches more than one building block only in the situation where one building block is coupled to a second building block as a dimer. The present claims require each building block to be independently coupled to a single spot or a region of the solid surface.

Furthermore, the present claims require the building blocks to be covalently, ionically, or hydrophobically coupled to the solid support. In Lahiri, the proteins in each microspot are membrane-bound, but are not otherwise covalently immobilized on the array surface.

Accordingly, based on the foregoing differences, Applicants respectfully submit that the Lahiri reference neither teaches nor suggests the presently claimed methods, and withdrawal of this rejection is respectfully requested.

Double Patenting

Claims 1–3, 10–15 and 80 were provisionally rejected for non-statutory obviousness-type double patenting over claims 85–105 of copending U.S. Application No. 10/244,727; claims 78–92 and 94–96 of copending Application No. 10/727,059 and claims 78, 79, 84, 90 and 96-102 of copending Application No. 10/706,505; and claims 1-7, 8 and 9 of copending Application No. 10/813,568. Applicants respectfully traverse the rejection.

Without acquiescing to the rejection and solely to expedite allowance of the present claims, a Terminal Disclaimer is submitted herewith. Applicants submit that said Terminal Disclaimer obviates the rejection. Applicants respectfully request withdrawal of this rejection.

SUMMARY

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
(612) 332-5300

Date: 15 May '07

Mark T. Skoog
Reg. No. 40,178

MTS:HLV:dc:kf

23552
PATENT TRADEMARK OFFICE